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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,834	02/16/2006	Jonathan Michael Blackburn	27353-513-US1	8870

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EXAMINER	
TSAY, MARSHA M	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,834	BLACKBURN ET AL.	
	Examiner	Art Unit	
	Marsha M. Tsay	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-42 and 44-77* is/are pending in the application.

4a) Of the above claim(s) *45-70 and 72-77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-42,44 and 71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 11, 2008 has been entered.

Claims 1-39, 43 are canceled. Claims 45-70, 72-77 are withdrawn. Claims 40-42, 44, 71 are currently under examination.

Applicants' arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous Office actions are hereby withdrawn.

Priority: The priority date is October 25, 2002.

Objections and Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-42, 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are directed to a method of detecting a protein of interest

comprising ble fusion protein wherein said ble fusion protein is an expression and folding marker and/or an affinity tag.

The specification does not contain disclosure for which proteins of interest. The genus of proteins that comprise a protein of interest is a large variable genus. Therefore, many functionally unrelated proteins are encompassed within the scope of these claims. To satisfy the written description aspect of 35 U.S.C. 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. The specification appears to disclose a Sh ble fusion protein as a protein of interest which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised interim guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 40-42, 44, 71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 40-44, 71 are rejected under 112 first paragraph because it refers to a protein only by function.

The court of Appeals for the Federal Circuit has recently held that such a general definition does not meet the requirements of 35 U.S.C. 112, first paragraph. "A written description of an invention involving chemical genus, like a description of a chemical species, requires a precise definition, such as be structure, formula {or} chemical name, of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.,* 1997 U.S. App. LEXIS 18221, at *23, quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). The court held that "in claims involving chemical materials, generic formulae usually indicate with specificity what generic claims encompass. One skilled in the art can distinguish such a formula fro others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish it from others. One skilled in the art therefore cannot, as one can do with a fully described genus visualize the identity of the members of the genus". Here, Applicant is claiming a product by what it does, i.e. function, rather than what it is (in terms of structure).

In their remarks, Applicants assert that claims 40-42, and 44 are amended to clarify that the ble fusion proteins may be used as an affinity tag to detect the protein of interest and to determine the folding state of the detected protein. Applicant's arguments have been fully considered but they are not persuasive.

As currently amended, it is unclear how the ble fusion protein is to be used in a method for detecting a protein of interest. Further, the ble fusion protein is still referred to by function only, i.e. an expression and folding marker.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 40-42, 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 40 and its dependent claims are drawn to a method of detecting a protein of interest comprising ble fusion protein wherein said ble fusion protein is an expression and folding marker and/or an affinity tag. The instant claims are incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. It is unclear if the protein of interest comprises said ble fusion protein or if the ble fusion protein is used to detect a protein of interest and how said ble fusion protein is used to detect said protein of interest or if the instant method is drawn to a method of detecting a ble fusion protein, it is unclear how the ble fusion protein is to be detected. In view of the specification, the instant

invention appears to be directed to a method of detecting a ble fusion protein comprising immobilizing said protein on a bleomycin coated surface. Further clarification is requested.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 40-41, 44 are rejected under 35 U.S.C. 102(b) as being anticipated by Gautier et al. (1996 Experimental Cell Research 224: 291-301; previously cited). Gautier et al. teach fusion genes carrying *Drosophila* alcohol dehydrogenase (Dro-ADH) fused to Sh ble were expressed in mammalian cells (p. 292, p. 295). Gautier et al. teach Dro-ADH was fused to the N- terminus or C-terminus of Sh ble, as well as a tandem gene carrying Sh ble gene fused with ADH sequences localized at both ends, and their expression (Fig. 3, p. 296 col. 2; claims 40-41, 44).

Claims 40-41, 44 remain rejected under 35 U.S.C. 102(b) as being anticipated by Bennett et al. (1998 BioTechniques 24(30): 478-482; previously cited). The instant methods are indefinite for the reasons noted in the 112, 2nd paragraph, rejections above. Claim 41 has been interpreted as a method for detecting a protein of interest comprising using a ble fusion protein for the purposes of prior art.

Bennett et al. teach a ble fusion protein comprising green fluorescent protein (GFP) and the Zeocin™-resistance gene Sh ble that can be used for visual screening and selection of

transfected mammalian cells (p. 478; claims 40-41, 44). Bennett teach western blot experiments of cells transfected with GFP-Sh ble fusion protein (p. 481; claims 40-41, 44).

In their remarks, Applicants assert Bennett relates to fusions to generate a bifunctional protein for the identification and selection of transfected mammalian cells. This bifunctional protein was aimed to determine transient transfection efficiencies in tissue culture cells using fluorescence microscopy carrying phleomycin resistance and Drosophila alcohol dehydrogenase reporter properties and their subsequent application in retroviral vectors. However, Bennett does not teach, disclose, or suggest the capture and/or binding of she ble fusion protein on a solid substrate via the she ble antibiotic binding pocket. Furthermore, Bennett does not relate to the She *ble* unusual property of stoichiometric antibiotic resistance wherein the mechanism of action is antibiotic binding rather than catalytic breakdown of the antibiotic. Due to these deficiencies, Bennett fails to enable instant method of detecting a protein of interest comprising ble fusion protein wherein said ble_fusion protein is an expression and folding marker and/or an affinity tag. Applicant's arguments have been fully considered but they are not persuasive.

As currently amended, it is unclear what the method of claim 40 is directed to. Applicants assert that Bennett does not teach, disclose, or suggest the capture and/or binding of she ble fusion protein on a solid substrate via the she ble antibiotic binding pocket; however, the instant claims do not recite these components of the invention. Therefore, claim 41 has been given its broadest and most reasonable interpretation, which is a method for detecting a protein of interest comprising a ble fusion protein. Bennett et al. teach a ble fusion protein can be

detected by antibodies and therefore, is believed to be relevant art in view of the indefiniteness of claim 40.

Claims 40-41, 44 remain rejected under 35 U.S.C. 102(b) as being anticipated by Baron et al. (1992 Gene 114(2): 239-243; previously cited). The instant methods are indefinite for the reasons noted in the 112, 2nd paragraph, rejections above. Claim 41 has been interpreted as a method for detecting a protein of interest comprising using a ble fusion protein for the purposes of prior art.

Baron et al. teach the Sh ble gene, conferring resistance to phleomycin, was fused in frame to both the 3' and 5' ends of *E. coli* lacZ gene in order to generate a bifunctional β-galactosidase::phleomycin-resistance fusion protein as a potential marker for eukaryotic cells (p. 239-240; claims 40-41, 44). In western blotting experiments performed on lysates of pUT97 and pUT98 transformants, protein band of 130 kDa was revealed with both anti-Ble and anti-βGal antibodies (p. 241; claims 40-41, 44).

In their remarks, Applicants assert that Baron demonstrates the bifunctionality of She ble fusion 130 Kda hybrid protein in E.coli and in the fungus and Tolypocladium geodes. The Baron system appears to be a potentially useful tool for the direct selection of transformants in a wide variety of prokaryotic and eukaryotic hosts. However, Barron does not does not teach, disclose, or suggest the capture and/or binding of She ble fusion protein on a solid substrate via the She ble antibiotic binding pocket. Barton does not relate to the She ble unusual property of stoichiometric antibiotic resistance wherein the mechanism of action is antibiotic binding rather

than catalytic breakdown of the antibiotic. Due to these deficiencies, Barron fails to enable instant method of detecting a protein of interest comprising *ble* fusion protein wherein said ble fusion protein is an expression and folding marker and/or an affinity tag. Applicant's arguments have been fully considered but they are not persuasive.

As currently amended, it is unclear what the method of claim 40 is directed to. Applicants assert that Barron does not does not teach, disclose, or suggest the capture and/or binding of She ble fusion protein on a solid substrate via the She ble antibiotic binding pocket; however, the instant claims do not recite these components of the invention. Therefore, claim 41 has been given its broadest and most reasonable interpretation, which is a method for detecting a protein of interest comprising a ble fusion protein. Baron et al. teach a ble fusion protein can be detected by antibodies and therefore, is believed to be relevant art in view of the indefiniteness of claim 40.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 42, 71 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Blackburn et al. (WO 0227327; previously cited) in view of Bennett et al. (1998 BioTechniques 24(30): 478-482; previously cited). Blackburn et al. teach methods of producing proteins in which one or more domains are full length and correctly folded and which are each tagged at either the N- or C-terminus with one or more marker moieties (p. 1 lines 1-5). The methodology

allows proteins to be "tagged" with a common marker, wherein the "tag" can be used to impart commonality and specificity to downstream immobilization and purification procedures (p. 3 lines 20-28). The marker moieties used to "tag" the proteins can be a peptide sequence, i.e. hexa-histidine tag, an antibody epitope, and/or a protein domain (p. 5 lines 14-18). On pages 15-17, Blackburn et al. teach the expression of the tagged protein and its uses upon purification.

The teachings of Bennett et al. are outlined above.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to create a "tagged" Ble fusion protein by substituting a hexa-histidine tag disclosed by Blackburn et al. for the GFP reporter protein disclosed by Bennett et al. and purify the protein by Zeocin selection (claims 42, 71). One of ordinary skill would recognize that an affinity tag, i.e. hexa-histidine tag, and GFP are both marker moieties that can be used to generate fusion proteins for purification and/or visualization of selected proteins.

Applicant's arguments have been fully considered but they are not persuasive.

The Blackburn et al. and Bennett et al. references are believed to be relevant art for the same reasons noted above.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha M. Tsay whose telephone number is (571)272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maryam Monshipouri/

Primary Examiner, Art Unit 1656

March 21, 2008